PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15656-10PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CA2004/000697	International filing date *(day/month/year)* 07.05.2004	Priority date *(day/month/year)* 09.05.2003
International Patent Classification (IPC) or national classification and IPC A61K38/40		
Applicant TRANSFERT PLUS et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.03.2005	20.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Page, M Telephone No. +49 89 2399-7322

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000697

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-10, 12-37, 39-58	as originally filed
11, 38	received on 18.03.2005 with letter of 09.03.2005

Sequence listings part of the description, Pages

1-12	as originally filed

Claims, Numbers

1-54	as originally filed

Drawings, Sheets

1-29	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000697

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-17,20,21,27-31,36-38,40-46

because:

☒ the said international application, or the said claims Nos. 1-17,20,21,27-31,36-38,40-46 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000697

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-54
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-3,8,9,18-21,23,28,30,31,42-54
	No:	Claims	4-7,10-17,22,24-27,29,32-41
Industrial applicability (IA)	Yes:	Claims	18,19,22-26,32-35,39,47-54
	No:	Claims	1-17,20,21,27-31,36-38,40-46: Opinion reserved

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

The application concerns the therapeutic application of melanotransferrin, also known as MTf or p97. The Applicant has uncovered the molecular mechanism by which this protein acts in angiogenesis and makes use of this in approaching a number of clinical problems.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 **Claims 1-17,20,21,27-31,36-38,40-46** are all considered to directly or covertly constitute methods of treatment. No unified criteria exist in the PCT Contracting States on the question whether methods of treatment are industrially applicable, as they are not considered to be industrially applicable in the EPC. No opinion can be given, therefore, on the industrial applicability of these claims.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: SALA ROBERTA ET AL: "The human melanoma associated protein melanotransferrin promotes endothelial cell migration and angiogenesis in vivo." EUROPEAN JOURNAL OF CELL BIOLOGY, vol. 81, no. 11, November 2002 (2002-11), pages 599-607, XP002300166 ISSN: 0171-9335

D2: US-B-6 455 4941 (JEFFERIES WILFRED A ET AL) 24 September 2002 (2002-09-24)

D3: DEMEULE MICHEL ET AL: "Regulation of plasminogen activation: A role for melanotransferrin (p97) in cell migration." BLOOD, vol. 102, no. 5, 1 September 2003 (2003-09-01), pages 1723-1731, XP002300165 ISSN: 0006-4971

D4: US 2002/119095 A1 (BROOKS ROBERT CHARLES ET AL) 29 August 2002 (2002-08-29)

V.2 **Novelty - Art.33(1) and (2) PCT:**

V.2.1 The prior art identifies p97 and antibodies directed thereto as being useful as a delivery protein or as a pro-angiogenic factor, and diagnostic applications respectively. None of the cited documents, however, discloses the physiological role of p97 now attributed to it by the Applicants and so these documents are not considered to disclose the claimed subject matter.

V.3 **Inventive Step - Art.33(1) and (3) PCT:**

V.3.1 In direct contradiction of the application, D1 teaches that p97 is a pro-angiogenic factor, stimulating and not inhibiting cell migration. The closing sentence of the application suggests that "[l]imiting the pro-angiogenic activity of MTf may therefore provide a method to decrease the vascularisation of tumours and therefore limit tumour progression or growth". Confronted with this suggestion, the skilled person would look for available potential p97 antagonists. Antibodies are well known in the art for their occasional agonistic as well as antagonistic activity by virtue of their binding to ligand binding sites and either mimicking the ligand or allostearically preventing the ligand from binding a given receptor.

V.3.2 The prior art is awash with references to anti-p97 antibodies (see particularly cited passages of D2 and D4). The IPEA submits that it would be obvious to the skilled person to investigate whether or not the known antibodies possess the highly desirable anti-angiogenic properties proposed in D1 and thus inventive step cannot be acknowledged for claims pertaining to the inhibition of cell migration and angiogenesis (**claims 4-7,10-17,22,24-27,29,32-41**).

V.3.3 It should be noted that the obviousness of looking to anti MTf antibodies as potential antiangiogenic reagents is not dependent upon whether MTf is agonistic or antagonistic to angiogenesis. The mere recognition that the protein is involved in blood vessel formation would be sufficient to strongly motivate the skilled person to examine the ability of the known antibodies to antagonise the previously

identified pro-angiogenic effect.

V.3.4 It is noted that D1 cannot be considered to fairly suggest that p97 promotes plasminogen activation or fibrinolysis.

Re Item VII

Certain defects in the international observation

VII.1 D1 contradicts the application in that it identifies soluble p97 as promoting cell migration and angiogenesis. The only plausible way to explain the contradictory effects of p97 in the two documents is that the activity of p97 is in some way dependent on the environment, be it the cell type or the experimental conditions. The Applicant has submitted that the experimental evidence provided in D1 is restricted to p97 trapped in a matrix, whereas the application deals with soluble p97. The claims should be limited to indicate that protection is only sought for soluble p97 and methods using the same, insofar as this is permitted within the scope of the application as filed. Other subject matter is considered to offend the support requirements of Articles 5 and 6 PCT (**claims 3, 18, 20-22, 27-29, 31, 32 and 36-51**).

VII.2 The Applicants have shown that the monoclonal antibody L235 interacts with p97 in a way that modifies the activity of the protein. However, it cannot be expected that other mAbs have the same effect as they will have distinct binding sites. The Applicants have not demonstrated that any of the other claimed antibodies have a similar desired effect to that of L235 and the application does not teach the skilled person how to arrive at such antibodies, e.g. by defining epitopes susceptible to blocking. Claims directed to either undisclosed antibodies or antibodies other than L235 should be restricted in scope to L235 in order to ensure that the claimed subject matter is properly supported (Article 6 PCT).

VII.3 The terms "L235", "HybC", "HybE", "HybF", "9B6" and "2C7" are not defined in the description in any technically meaningful way in the application. These antibodies are not among those listed on page 14 of the description. As a result, claims referring to such antibodies are considered to lack clarity according to Article 6 PCT.